PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 21 February 2001 (21.02.01)	
International application No. PCT/US00/15161	**Applicant's or agent's file reference** DRE-0027
International filing date (day/month/year) 01 June 2000 (01.06.00)	**Priority date** (day/month/year) 01 June 1999 (01.06.99)
Applicant BASUDE, Raghuveer et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

27 December 2000 (27.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Olivia TEFY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 December 2000 (07.12.2000)

PCT

(10) International Publication Number
WO 00/72757 A1

(51) International Patent Classification[7]: A61B 8/00, A61K 9/16

(21) International Application Number: PCT/US00/15161

(22) International Filing Date: 1 June 2000 (01.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/136,965 1 June 1999 (01.06.1999) US

(71) Applicant *(for all designated States except US)*: **DREXEL UNIVERSITY** [US/US]; 32nd & Chestnut Streets, Philadelphia, PA 19104 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BASUDE, Raghuveer** [IN/US]; 3604 Spring Garden Street, Apartment D6, Philadelphia, PA 19104 (US). **WHEATLEY, Margaret, A.** [US/US]; 7 Camby Chase, Media, PA 19063 (US).

(74) Agents: **LICATA, Jane, Massey** et al.; Law Offices of Jane Massey Licata, 66 E. Main Street, Marlton, NJ 08053 (US).

(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/72757 A1

(54) Title: SURFACE STABILIZED MICROBUBBLES FOR USE IN ULTRASOUND CONTRAST AND DRUG DELIVERY AGENTS

(57) Abstract: Surface stabilized microbubbles produced from microparticles or objects having a hydrophobic surface and gas bubbles which attach to or encapsulate the microparticle or surface of the object for use as ultrasound contrast and drug delivery agents are provided.

TENT COOPERATION TREATY

PCT

14

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
DRE-0027		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/15161	01 June 2000 (01.06.2000)	01 June 1999 (01.06.1999)
International Patent Classification (IPC) or national classification and IPC		
IPC(7): A61B 8/00; A61K 9/16 and US Cl.: 424/9.52, 489; 600/458		
Applicant		
DREXEL UNIVERSITY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27 December 2000 (27.12.2000)	01 August 2001 (01.08.2001)
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Michael G. Hartley Telephone No. (703) 308-1235

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International Application No.
PCT/US00/15161

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-11 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 12-14, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages 1, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	8	YES
	Claims	1-7 and 9-14	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-14	NO
Industrial Applicability (IA)	Claims	1-14	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS (Rule 70.7)
Please See Continuation Sheet

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

V. 2. Citations and Explanations:

Claims 1-7 and 10-14 lack novelty under PCT Article 33(2) as being anticipated by Rasor.

Rasor discloses a composition for ultrasound imaging comprising a microparticle having a hydrophobic surface (such as, a lipophilic surfactant) and a gas microbubble, see column 6, lines 3-11. The gas microbubble attaches or is contact with the microparticle, see column 6, line 57. The compositions are prepared by methods including storing the microparticle in a gaseous environment and introducing the microparticles into a liquid, see columns 9-10 and examples. The compositions contain a drug or an object, such as, the gaseous material as a contrast agent.

Claims 1-7 and 9-14 lack novelty under PCT Article 33(2) as being anticipated by Schneider.

Schneider discloses a composition for ultrasound imaging comprising a microparticle having a hydrophobic surface (such as, a liposome) and microbubbles which are associated therewith, in that the liposomes stabilize the microbubbles, see column 4, lines 6-36. The compositions are prepared by a method of storing the liposomes in a gaseous environment and introducing the liposomes into a liquid, see column 4, lines 37-55. The compositions may further include drugs, such as radionuclides for nuclear medicine, see column 10, lines 3-5, as well as, a targeting moiety, see column 9, lines 36-66.

Claims 1-14 lack an inventive step under PCT Article 33(3) as being obvious over Rasor or Schneider in view of Unger.

Rasor and Schneider disclose compositions comprising a microparticle and microbubble for methods of ultrasound as discussed above.

Rasor and Schneider fail to disclose that the compositions may be used for drug delivery by insonating the desired site in the patient to rupture the microbubble thereby releasing a drug.

Unger discloses compositions comprising microbubbles that are useful for both ultrasound imaging and drug delivery, see abstract and column 35, lines 4-5. Unger teaches that the microbubbles may further comprise various drugs which are released by insonation to provide the advantage of site-specific delivery to a desired site, see column 35, lines 29+.

It would have been obvious to one of ordinary skill in the art to use the compositions disclosed by Rasor or Schneider for drug delivery by insonating the microbubbles at a desired site *in vivo* because Unger teaches that gas-filled microbubbles may further contain various drugs to yield a drug delivery means having the advantage of site-specific delivery by insonating the microbubbles at a desired site *in vivo*. One of ordinary skill in the art would have been motivated to employ the drug delivery methods disclosed by Unger using the compositions disclosed by Rasor and Schneider to obtain a composition which is useful for both ultrasound imaging and site-specific therapy using a single administration.

Applicant's arguments filed 18 June 2001 have been considered, but are not persuasive.

Applicant asserts that the microparticles taught by Rasor are only lipophilic and are not taught to have affinity for specific gases.

This is not found persuasive because the instant claims are drawn to microparticles which have a hydrophobic surface (e.g., lipophilic)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

or an affinity for a specific gas. Thus, the affinity for a specific gas is not required by the instant claims.

Applicant asserts that nowhere does Rasor teach a gas microbubble attached to or encapsulating a microparticle.

This is not found persuasive because Rasor teaches that the microbubble and microparticles are in intimate association (e.g., attached), see column 6, line 57.

Applicant asserts that the microparticles disclosed by Rasor require both a fatty acid and a non-surfactant solid.

The relevance of this argument is not seen, as Rasor discloses compositions as claimed, for example, microparticles having a hydrophobic surface which are attached to microbubbles.

Applicant asserts that Schneider fails to teach or suggest a gas microbubble that attaches or encapsulates a microparticle.

This is not found persuasive because Schneider teaches a composition wherein liposomes are attached to the surface of microbubbles to stabilize the microbubbles, and such stabilization would necessitate attachment of the microbubbles to the liposomes.

Applicant asserts that there is no suggestion that the system disclosed by Unger would work with microbubbles that are not heat activated.

This is not found persuasive given the teaching of Unger that ultrasound contrast agents may include a therapeutic agent to impart a combined diagnostic and therapeutic effect with the benefit of site activated (or site specific) delivery. Unger teaches that the microparticles are specifically formulated for temperature activation, wherein the temperature activation imparts site specificity to the delivery systems. One of ordinary skill in the art would have been motivated to modify the compositions disclosed by Rasor and/or Schneider to include heat activation in order to gain the advantage of site specific delivery.

Claim 8 meets the criteria set out in PCT Article 33(2), because the prior art does not teach compositions comprising a microparticle and microbubble for methods of drug delivery by insonating the desired site in the patient to rupture the microbubble thereby releasing a drug.

Claims 1-14 meet the criteria set out in PCT Article 33(4), because the claimed compositions and methods are useful for ultrasound imaging and drug delivery to a selected site *in vivo*.

---------- NEW CITATIONS ----------

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
JANE MASSEY LICATA
LAW OFFICES OF JANE MASSEY LICATA
66 E. MAIN STREET
MARLTON, NJ 08053

NP= 12/1/01
Docket System ✓
Status Report ✓
Docket Book ✓

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing (*day/month/year*)	30 AUG 2001

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
DRE-0027	

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US00/15161	01 June 2000 (01.06.2000)	01 June 1999 (01.06.1999)

Applicant

DREXEL UNIVERSITY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Michael G. Hartley
Facsimile No. (703)305-3230	Telephone No. (703) 308-1235

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
DRE-0027		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/15161	01 June 2000 (01.06.2000)	01 June 1999 (01.06.1999)
International Patent Classification (IPC) or national classification and IPC		
IPC(7): A61B 8/00; A61K 9/16 and US Cl.: 424/9.52, 489; 600/458		
Applicant		
DREXEL UNIVERSITY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27 December 2000 (27.12.2000)	01 August 2001 (01.08.2001)
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Michael G. Hartley Telephone No. (703) 308-1235

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US 5161

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-11 as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☒ the claims:
pages 12-14 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☒ the drawings:
pages 1 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*
*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	8	YES
	Claims	1-7 and 9-14	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-14	NO
Industrial Applicability (IA)	Claims	1-14	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS (Rule 70.7)
Please See Continuation Sheet

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

V. 2. Citations and Explanations:

Claims 1-7 and 10-14 lack novelty under PCT Article 33(2) as being anticipated by Rasor.

Rasor discloses a composition for ultrasound imaging comprising a microparticle having a hydrophobic surface (such as, a lipophilic surfactant) and a gas microbubble, see column 6, lines 3-11. The gas microbubble attaches or is contact with the microparticle, see column 6, line 57. The compositions are prepared by methods including storing the microparticle in a gaseous environment and introducing the microparticles into a liquid, see columns 9-10 and examples. The compositions contain a drug or an object, such as, the gaseous material as a contrast agent.

Claims 1-7 and 9-14 lack novelty under PCT Article 33(2) as being anticipated by Schneider.

Schneider discloses a composition for ultrasound imaging comprising a microparticle having a hydrophobic surface (such as, a liposome) and microbubbles which are associated therewith, in that the liposomes stabilize the microbubbles, see column 4, lines 6-36. The compositions are prepared by a method of storing the liposomes in a gaseous environment and introducing the liposomes into a liquid, see column 4, lines 37-55. The compositions may further include drugs, such as radionuclides for nuclear medicine, see column 10, lines 3-5, as well as, a targeting moiety, see column 9, lines 36-66.

Claims 1-14 lack an inventive step under PCT Article 33(3) as being obvious over Rasor or Schneider in view of Unger.

Rasor and Schneider disclose compositions comprising a microparticle and microbubble for methods of ultrasound as discussed above.

Rasor and Schneider fail to disclose that the compositions may be used for drug delivery by insonating the desired site in the patient to rupture the microbubble thereby releasing a drug.

Unger discloses compositions comprising microbubbles that are useful for both ultrasound imaging and drug delivery, see abstract and column 35, lines 4-5. Unger teaches that the microbubbles may further comprise various drugs which are released by insonation to provide the advantage of site-specific delivery to a desired site, see column 35, lines 29+.

It would have been obvious to one of ordinary skill in the art to use the compositions disclosed by Rasor or Schneider for drug delivery by insonating the microbubbles at a desired site *in vivo* because Unger teaches that gas-filled microbubbles may further contain various drugs to yield a drug delivery means having the advantage of site-specific delivery by insonating the microbubbles at a desired site *in vivo*. One of ordinary skill in the art would have been motivated to employ the drug delivery methods disclosed by Unger using the compositions disclosed by Rasor and Schneider to obtain a composition which is useful for both ultrasound imaging and site-specific therapy using a single administration.

Applicant's arguments filed 18 June 2001 have been considered, but are not persuasive.

Applicant asserts that the microparticles taught by Rasor are only lipophilic and are not taught to have affinity for specific gases.

This is not found persuasive because the instant claims are drawn to microparticles which have a hydrophobic surface (e.g., lipophilic)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

or an affinity for a specific gas. Thus, the affinity for a specific gas is not required by the instant claims.

Applicant asserts that nowhere does Rasor teach a gas microbubble attached to or encapsulating a microparticle.

This is not found persuasive because Rasor teaches that the microbubble and microparticles are in intimate association (e.g., attached), see column 6, line 57.

Applicant asserts that the microparticles disclosed by Rasor require both a fatty acid and a non-surfactant solid.

The relevance of this argument is not seen, as Rasor discloses compositions as claimed, for example, microparticles having a hydrophobic surface which are attached to microbubbles.

Applicant asserts that Schneider fails to teach or suggest a gas microbubble that attaches or encapsulates a microparticle.

This is not found persuasive because Schneider teaches a composition wherein liposomes are attached to the surface of microbubbles to stabilize the microbubbles, and such stabilization would necessitate attachment of the microbubbles to the liposomes.

Applicant asserts that there is no suggestion that the system disclosed by Unger would work with microbubbles that are not heat activated.

This is not found persuasive given the teaching of Unger that ultrasound contrast agents may include a therapeutic agent to impart a combined diagnostic and therapeutic effect with the benefit of site activated (or site specific) delivery. Unger teaches that the microparticles are specifically formulated for temperature activation, wherein the temperature activation imparts site specificity to the delivery systems. One of ordinary skill in the art would have been motivated to modify the compositions disclosed by Rasor and/or Schneider to include heat activation in order to gain the advantage of site specific delivery.

Claim 8 meets the criteria set out in PCT Article 33(2), because the prior art does not teach compositions comprising a microparticle and microbubble for methods of drug delivery by insonating the desired site in the patient to rupture the microbubble thereby releasing a drug.

Claims 1-14 meet the criteria set out in PCT Article 33(4), because the claimed compositions and methods are useful for ultrasound imaging and drug delivery to a selected site *in vivo*.

---------- NEW CITATIONS ----------

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: JANE MASSEY LICATA
LAW OFFICES OF JANE MASSEY LICATA
66 E. MAIN STREET
MARLTON NJ 08053

Docket System √
Status Report √
Docket Book √
10/17/00 AGS

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference DRE-0027	Date of Mailing *(day/month/year)* 14 AUG 2000 **FOR FURTHER ACTION** **See paragraphs 1 and 4 below**
International application No. PCT/US00/15161	International filing date *(day/month/year)* 01 JUNE 2000
Applicant DREXEL UNIVERSITY	

1. [X] The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 *bis* 1 and 90 *bis* 3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MICHAEL G. HARTLEY Telephone No. (703) 308-1235

Form PCT/ISA/220 (July 1998)*

(See notes on accompanying sheet)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/15161

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61B 8/00; A61K 9/16
US CL :424/9.52, 489; 600/458

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/9.52, 9.5, 9.51, 489, 450, 490; 600/458, 441

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EAST
search terms: microbubbles, gasbubbles, microparticles, ultrasound, echography, drug, therapeutic, delivery.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,141,738 A (RASOR ET AL) 25 August 1992, see column 6, lines 3-11 and columns 9-11.	1-14
Y	US 5,271, 928 A (SCHNEIDER ET AL) 21 December 1993, see columns 4-5.	1-14
Y	US 5,542,935 A (UNGER ET AL) 06 August 1996, see abstract and column 35.	1-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 17 JULY 2000	Date of mailing of the international search report 14 AUG 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MICHAEL G. HARTLEY Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)*

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference DRE-0027	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US00/15161	International filing date *(day/month/year)* 01 JUNE 2000	(Earliest) Priority Date *(day/month/year)* 01 JUNE 1999
Applicant DREXEL UNIVERSITY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (See Box II).

4. With regard to the **title**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/15161

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61B 8/00; A61K 9/16
US CL :424/9.52, 489; 600/458
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/9.52, 9.5, 9.51, 489, 450, 490; 600/458, 441

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EAST
search terms: microbubbles, gasbubbles, microparticles, ultrasound, echography, drug, therapeutic, delivery.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,141,738 A (RASOR ET AL) 25 August 1992, see column 6, lines 3-11 and columns 9-11.	1-14
Y	US 5,271, 928 A (SCHNEIDER ET AL) 21 December 1993, see columns 4-5.	1-14
Y	US 5,542,935 A (UNGER ET AL) 06 August 1996, see abstract and column 35.	1-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 17 JULY 2000	Date of mailing of the international search report 14 AUG 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MICHAEL G. HARTLEY Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)*